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<b>14. ABSTRACT</b> In this article, we summarize how psychopharmaceuticals for potential military operational use may be evaluated based on their effects on performance and safety, and introduce two manuscripts: the first (Caldwell and Caldwell) addressing the operational use of fatigue countermeasures; and the second (Rowland) discussing the potential operational use and limitations of ketamine as a field analgesic. Fatigue countermeasures are usually employed by a relatively small number of military members engaged in sustained or continuous operations when sleep is not an option. Clinical treatments are available at any time as required to treat medical conditions. The issue of importance for the operational community, with regard to both clinical use of psychopharmaceuticals and performance maintenance through fatigue countermeasures, should be whether the medication impairs operationally relevant performance, assuming the disorder for which the medication is prescribed does not in itself prohibit operational duties. Applied research paradigms are generally discussed for assessing and transitioning pharmaceutical compounds from the laboratory to the operational environment. Tier 1 focuses on quantifying the impact of stressors and interventions in healthy members of the general population, while Tier 2 testing would use military or operationally matched volunteers in simulated or actual field environments. The section papers address two areas of operational relevance—the Caldwell and Caldwell paper presents guidelines for the use of fatigue countermeasures, and the Rowland paper discusses the potential effects of ketamine, an agent intended to replace morphine as a battlefield analgesic, on cognition.						
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# Assessing Psychoactive Pharmaceuticals and Transitioning Pharmacological Fatigue Countermeasures into Operational Environments

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Herein we summarize a discussion on the topic of how psychopharmaceuticals for potential military operational use may be evaluated based on their effects on performance and safety, and introduce two manuscripts: the first (Caldwell and Caldwell); 1) addressing the operational use of fatigue countermeasures; and the second (Rowland); 3) discussing the potential operational use and limitations of ketamine as a field analgesic. Fatigue countermeasures are usually employed by a relatively small number of military members engaged in sustained or continuous operations when sleep is not an option. Clinical treatments are available at any time as required to treat medical conditions. The issue of importance for the operational community, with regard to both clinical use of psychopharmaceuticals and performance maintenance through fatigue countermeasures, should be whether the medication impairs operationally relevant performance, assuming the disorder for which the medication is prescribed does not in itself prohibit operational duties. Applied research paradigms are generally discussed for assessing and transitioning pharmaceutical compounds from the laboratory to the operational environment. Tier 1 focuses on quantifying the impact of stressors and interventions in healthy members of the general population, while Tier 2 testing would use military or operationally matched volunteers in simulated or actual field environments. The section papers address two areas of operational relevance—the Caldwell and Caldwell paper presents guidelines for the use of fatigue countermeasures, and the Rowland paper discusses the potential effects of ketamine, an agent intended to replace morphine as a battlefield analgesic, on cognition.

**Keywords:** fatigue countermeasures, pharmacologic countermeasures, psychotropic, operations, pharmaceuticals, pharmacology.

**P**SYCHOPHARMACOLOGICAL agents routinely in use by military personnel in network-centric environments include both fatigue countermeasures and clinical treatments. Fatigue countermeasures, such as performance-enhancing and sleep-enhancing agents, are usually employed by a relatively small number of warfighters engaged in sustained or continuous operations when sleep is not an option. Clinical treatments are available at any time to all warfighters as required to treat medical conditions.

Regarding the clinical use of psychopharmacologic treatments for medical conditions in warfighters, in most circumstances the use of psychotropic compounds is not known to their supervisors—as long as operational performance of the individual and the team is

maintained, the supervisor has no need to know. In aviation, flight surgeons prescribing psychotropic medications follow strict guidelines regarding the compatibility of the medication with flight duties, but each service has different regulations, suggesting that the strict guidelines may be somewhat arbitrarily determined. The regulations grounding the aviator are well intentioned, to ensure safety of crew and aircraft, but if the crewmember is fit to serve but grounded based on regulation rather than need, the grounding action itself adversely impacts the operational performance of the individual and the unit as a whole. In many cases the grounding action is quite appropriate given the medication effect on the aviator.

The issue of importance for the operational community, with regard to both clinical and fatigue countermeasures usage of psychoactive agents, should not be whether an individual warrior is on a psychotropic medication, or which medication, but rather whether the psychotropic medication impairs or does not impair the cognitive and operationally relevant performance of the warfighter. In aviation environments, where the use of medication is carefully controlled, the flight surgeon has the authority to prescribe medication, but does not have the authority to return the aviator to flight status solely based on professional judgment applied to the effects of a clinically used medication on that individual aviator. With clinical use of psychotropic medications, regulations require grounding of the aviator for various periods of time, regardless of the diagnosis or the flight surgeon's determination of the aviator's ability to perform flight duties. For example, an aviator may be

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taking a low dose of an antidepressant for smoking cessation purposes. Smoking is not a condition that impairs cognitive performance, and the low dose antidepressant most likely would not impair cognitive performance, but the blanket regulations governing the use of the antidepressant treatment require the flight surgeon to ground the aviator. We in the medical community would be serving our patients poorly if we did not seek to redress regulations that require aviators to choose between taking a medication to help them stop smoking, but which would result in temporary loss of flight status, or choose to forsake an effective treatment in order to remain on flight status and continue to smoke.

The question that should be asked is does the treatment itself alter some aspect of operational performance, assuming circumstances in which the medical condition is either well controlled or in itself does not impair performance? For example, Russo suggests that aviator flight performance with regard to judgment, decision making, and higher order cognitive skills be the basis for approving the use of selective serotonin re-uptake inhibitors (SSRIs) in medical conditions that would not in themselves impair performance (4). With regard to the use of SSRIs in operational environments, Ireland suggests that flight surgeons could assess each aviator with appropriate ground testing prior to their engaging in flight tasks (2).

The network-centric battlefield is not one of defined geography, but one where warfighters battle from computers thousands of miles away from physical hostilities. Warfighters based outside of combat zones may fill prescriptions provided by civilian physicians at local pharmacies; they are no longer restricted to medications available in theater. Assessing the operational performance effects of classes of medications in both healthy and patient populations, and recommending usage guidelines based on sound knowledge of their effects on cognition would potentially improve the effectiveness of the military in several ways. The health of individual aviators would be improved if aviators considering treatment for medical conditions more often selected treatment that in itself would not ground them. The effectiveness of the unit as a whole would be maintained if aviators initiating a pharmacologic treatment could be returned to flight status at an earlier time. Primary care physicians outside of aviation could apply similar assessment techniques to ground- and sea-based warriors to keep operationally functional warfighters engaged in mission-essential, command-directed activities.

Flight surgeons are granted the authority to perform ground-based cognitive assessments prior to permitting flight duties with pharmacologic countermeasures because research performed in the past supports their decision-making processes. Performing the research to identify potential cognitive impairments in other classes of psychotropic agents would provide the scientific foundation necessary for flight surgeons and non-flight surgeons alike to apply professional judgment regarding the operational performance effects of clinical treatments. Providing primary care physicians

with the authority and tools to assess cognitive performance would potentially provide improved services to both aviators and non-aviators alike.

A consistent, valid, and user-focused approach is essential for transitioning research on the operational effects of psychoactive compounds from the laboratory to the field. There is an increased emphasis within the U.S. Army Medical Research and Materiel Command (USAMRMC), the Defense Advanced Research Projects Agency (DARPA), and the Air Force Research Laboratory (AFRL) to maximize coordination and standardization using across-laboratory assessment strategies. Studies must show clear relevance to the operational environment as this will ultimately guarantee that military operational communities are adequately served in all aspects of the military's applied research.

A two-tiered approach discussed at a DARPA workshop is outlined below, and proposes to optimize the transition of operationally useful interventions from the clinical realm to the battlefield in a way that is clearly meaningful to U.S. military personnel. Consideration of FDA and appropriate Federal regulations must be an integral part of the research and policy development process for use of already FDA-approved pharmaceutical compounds in operational environments. An emphasis on top-down, coordinated implementation strategies will maximize research efficiency and operational acceptance. An increased focus on advanced model development and validation will help to formulate and maintain a unified research approach that will ultimately result in new tools of significant use to leaders. More in-depth research into the complexities of higher level cognition/judgment and team vs. individual performance is necessary to meet the growing demands of today's complex battlefield operations. Improvements that are made to our research methodologies will ultimately help military personnel who confront the harsh realities of modern combat.

Following the USAMRMC-sponsored Florida workshop on "Cognitive Performance: The Future Force Warrior in a Network-Centric Environment," the subsequent DARPA-AFRL sponsored meeting was conducted in San Antonio, TX, on 21 September, 2004, to develop a consensus approach for transitioning FDA-approved fatigue countermeasures from the laboratory into military operational use. The product of that meeting, a consensus strategy for applied research to assess the operationally relevant aspects of pharmaceutical countermeasures that would be acceptable to the scientific community as well as military operators, leaders, and policy makers, is outlined in this paper. We acknowledge diverse expertise in the military and civilian research communities with regard to transitioning pharmacologic agents such as vaccines and antibiotics from the laboratory to the field. We hope to team with elements of this expert community for the purposes of applying the same successful approaches to transitioning psychoactive compounds.

The 21 September, 2004, San Antonio workshop specifically focused on one type of psychoactive compound, a countermeasure for sustaining performance in fatigued but otherwise normal military personnel in

combat environments. The outcomes may be more broadly applied to assessment of the operationally relevant aspects of psychoactive agents in general. Discussion focused on four main topics:

- 1) development of a standard, two-tiered transition path;
- 2) the importance of ensuring that the transition path is "top down" and at least somewhat uniformly applied across services;
- 3) the importance of the application, improvement, and validation of human performance/intervention models; and
- 4) the urgency of identifying and executing already existent paradigms and the development of metrics where none may exist to assess complex aspects of cognition such as team performance, judgment, and decision making.

For any pharmaceutical agent approved for clinical use, a great deal of information has already been assessed in specific patient populations. Although approval of a medication for clinical use permits its application to other conditions and in other populations, the effectiveness of the medication in other circumstances may not equal its effectiveness for the approved indications. With regard to the use of psychotropic agents in high intensity operational environments, there is an information shortfall on the effectiveness of compounds when used in healthy individuals placed into unusually stressful situations. Focused studies assessing the effectiveness of selected compounds under stresses simulating those found in operational environments should be made to ensure their effectiveness under the anticipated conditions.

Two communities with very different perspectives, the scientific/regulatory and the military operational communities, would have to be convinced of the safety and efficacy of new compounds. In instances where there is a close physician-patient (operator) relationship, such as in the aviation community, military decision makers may choose to promulgate policy that authorizes flight surgeons to prescribe drugs to support operational needs in "off-label" uses. In instances where such a close patient-physician relationship is not possible, such as with infantry personnel, the military must seek FDA approval for the field-based indication. In all cases we advocate only voluntary use of the pharmaceutical compounds as well as guidelines that clarify for both physicians and service members the circumstances under which the compounds may be used. In addition to scientifically proving the safety and efficacy of a potential pharmacological fatigue countermeasure in a military operational environment and adhering to FDA regulations, military commanders, in coordination with the military operational medical community, must clearly understand the operational benefits and risks associated with various compounds in order to design and implement appropriate policies for operational use. It is important to note that in the context of this meeting of applied researchers, the dis-

cussion of FDA regulatory and other in-depth policy issues were limited.

#### *Two-Tiered Transition Path*

Two tiers were proposed for assessing and transitioning pharmaceutical compounds from the laboratory to the operational environment.

*Tier 1:* Tier 1 focuses on quantifying the impact of stressors and interventions in healthy members of the general population using both validated performance tasks acceptable to the FDA and physiological measures. Studies in military or university laboratories in which healthy volunteers are evaluated under stressor conditions emulating those existent in operational environments would provide preliminary evidence for the efficacy and safety of the compound under those conditions. These studies should assess basic performance primarily using neurophysiological assessments (electroencephalographic, oculometric, and actigraphic indices), subjective surveys (Profile of Mood States, etc.), and cognitive performance tests such as the Multi-Attribute Task Battery, Psychomotor Vigilance Test, and Cambridge Neuropsychological Test Automated Battery, etc. When possible, task analyses should be used to assist in selecting battery subtasks that most closely match those required in specific operational situations. On completion of Tier 1 studies those compounds showing operationally safe and effective characteristics may be advanced to Tier 2.

*Tier 2:* Tier 2 testing would use military or operationally matched volunteers in simulated or actual field environments for performance on military tasks under stressful conditions. Usage of actual air- and ground-based mobile platforms for testing aircrew or vehicular drivers was deemed essential during this tier for establishing validity in the military operational community. Controlled studies conducted with high-fidelity simulators and, whenever possible, actual operational tests, are critical for the transition of the intervention into the real-world of military operations. Before pharmacologic agents are employed in operational environments, active-duty military volunteers (representative of the ultimate "end users") should be invited to participate in validation studies aimed at assessing both end-user acceptability and practicality. The closer that the operational context is emulated during these tests, the higher the level of safety and effectiveness that can be assured in the demanding situations routinely confronted by our military personnel.

For new interventions to be fully accepted by the military personnel in the field, it is necessary to balance scientific control and operational relevance (face validity). Operational tasks often are difficult to control and may not incorporate reliable, sensitive, or valid metrics. Therefore, second-tier testing may assess the impact of stressors and countermeasures on validated laboratory tasks, but does so in actual field environments using military personnel. An example of a metric that may be applied for this purpose is the Automated Neuropsychological Assessment Metric. At other times, it will be possible to evaluate independent variables in specially instrumented flight simulators/aircraft, in weapons

trainers, or in specially outfitted training/mission simulators (i.e., Airborne Warning and Controls System or AWACS, ground-based Command and Control, etc.). Operational personnel will be more likely to accept the results of a study if it is conducted using actual operators performing their missions (or some components of these tasks) in their normal training/work environment.

#### *Occupation-Specific Test Strategies*

At the San Antonio workshop, three military occupational groups were identified as primary customers for initial fielding of pharmacologic countermeasures research products: aviation, special operations ground forces, and Command and Control. Although there is some overlap of basic skills in these occupations, the tasks and environments for each group are very different. Validation of the safety and efficacy of a potential intervention in each specific operational environment is recommended. When possible, studies in specific contexts should build on past investigations in such a way that meaningful cross-study comparisons can be accomplished. For example, common experimental designs should be sought for all stimulant or hypnotic studies. New metrics to assess higher order cognitive elements such as team performance and decision making could be incorporated into designs as the tests are identified and validated.

*Aviation:* Fatigue countermeasures are available to augment the capability of aviators to remain awake and alert for extended periods of time; however, prior to fielding these measures in operational settings it is essential to: 1) fully understand the effects of sleep loss on aircrews' and pilots' physiological, psychological, and performance status; and 2) develop and validate proposed fatigue interventions in operationally relevant research environments. The most directly field-applicable methodology for aviation settings involves the testing of actual military pilots and aircrew members in high-fidelity simulations which include physiological monitoring, cognitive testing, subjective questionnaires, polysomnographic evaluations, and realistic flight simulations. Particular attention should be focused on examining aviation-relevant skills in high-fidelity, full-visual flight simulators and specially instrumented aircraft equipped with objective, computerized performance-monitoring capabilities.

*Special operations ground forces:* All aspects of cognitive performance are severely degraded during typical military ground operations involving substantial sleep loss. Other operational stressors such as heat, cold, high altitude, dehydration, and under-nutrition exacerbate these deficits. Tests that appear to have high operational relevance (face validity) such as marksmanship are often insensitive to the adverse effects of operational stressors and interventions known to be efficacious. Physical performance does not deteriorate as rapidly as cognitive performance as a consequence of sleep loss and many other operational stressors. Therefore, it is recommended that when physical performance is an outcome variable, tests that have a substantial cognitive component should also be used.

*Command and Control:* The approach to quantifying the effects of pharmacological adjuncts on Command and Control performance should also follow the tiered transition path approach presented above. Within that framework at least two types of test environments will likely be necessary. First, a simplified test environment should be used to assess the abilities of relative novices to perform the core functions of Command and Control. Here, the core tasks should be represented in an efficient and simplified manner to facilitate rapid learning and mastery. This strategy will allow for participant selection from non-specific populations, thus easing the participant recruitment process and allowing for greater generalizability of results. Of course, when using such synthetic environments, significant effort must be focused on linking test tasks to their actual job counterparts. This will allow for meaningful interpretation and application of the results to operators in the real world. Metrics which capture various levels of performance (process, outcome, individual, and team) need to be included, and metrics should capture both single process (e.g., ID SAM; identify surface-to-air missiles) and system-wide behaviors (e.g., entire 'kill chain'). Research conducted at this level can lead to rapid prototyping, allowing for "out-of-the-box" types of innovations. Second, high fidelity simulations should be used in exercises or operational test environments, if possible. Simulators (with critical measurement capabilities) should be linked to generate team and "team of teams" situations in which performance can be assessed during the conduct of typical operational scenarios that include best- and worst-case situations (i.e., high workload or reduced number of operators) in realistic environments (e.g., long hours, vibration).

#### *"Top-Down" Transition Path*

There is a clear need to develop a "top-down" requirement that mandates that the logical testing procedure outlined above be followed prior to introducing any new countermeasures into the operational environment. The highest levels of leadership should demand that such a strategy be used and then facilitate the accomplishment of comprehensive test programs rather than relying on individual scientists (or small groups of scientists) to: 1) formulate the work; 2) find the resources necessary to conduct the work; and 3) make the right connections between the operators and the laboratories needed to facilitate coordinated efforts that often are multifaceted and time consuming. In order to conduct operationally useful research, there must be clear investment on the part of the research community as well as specific components of the operational community to facilitate the investigational efforts.

A wide range of military and non-military organizations have need for information on human performance, the effects of stressors such as fatigue, and the efficacy of pharmacologic countermeasures. Academia, government, and military organizations possess unique facilities and capabilities to obtain information that could be applied to Tier 2 studies (or the modeling of results). There is a clear need to coordinate the interests and resources of these organizations to meet the top-town requirements for tran-

sitioning effective performance-enhancing/sustaining countermeasures from the laboratory into the military setting. Leadership support is vital as such coordination is often well beyond the capabilities of a single investigator or group of investigators.

### Modeling

Fatigue countermeasures and other types of applications-oriented experiments should be designed and conducted in such a way that the results will be immediately useful to not only operators, but also to those who construct the predictive models. With the right focus up front, it is possible to design studies so that the modeling of human performance under stressors and associated interventions can be systematically validated and improved. Appropriate models have the capacity to translate volumes of data into operationally useful tools that can allow leaders to perform the sorts of "what if" analyses critical for developing optimal work schedules and/or the most favorable strategies for applying performance-enhancing interventions. Well-designed and well-validated models can predict individual differences, optimum countermeasures, etc., for a variety of military-specific scenarios. However, to facilitate model design and evolutionary improvements, it is imperative that the modelers clearly identify the type of information needed from the research community to address these specific issues. Thus, there should be a high level of coordination between the investigator staffs and the modelers.

Modeling can also reveal gaps in data, detect optimal points in a proposed research schedule, and determine necessary measures to feed into the next generation model. Viewed in this way, research and modeling proceed as an integrative, iterative, and mutually supportive process. And, when the appropriate strategies are employed, each phase of model development can provide immediate "technology transition" to the operational community.

### Current Scientific Gaps

Although the complexity of the military operational environment continues to escalate exponentially, with missions increasingly relying on teams rather than individuals, relatively little research has been performed in the area of team performance assessment. Issues such as fatigue and the effects of interventions on higher-order cognitive function, decision making and judgment, or complex team interactions need to be addressed. In large part, the dearth of research in team performance assessment is due to the difficulty in creating tests that measure this type of performance, at least in a way that is repeatable over time without confounding effects. A major drawback to such higher-level assessments is that they are more susceptible to within-subjects or within-groups variability. To overcome this difficulty, greater sample sizes are required, leading to substantial increases in study-related costs (and often added problems in terms of subject recruitment). However, the fact that these problems exist does not alleviate the need for the research, and those in-

volved in studying the effects of operational problems and solutions for battlefield stressors must begin to apply additional effort toward ensuring that our research truly meets today's real-world challenges.

### Section Papers

The papers presented in this pharmacology section will address two areas of operational relevance—the first is the use of fatigue countermeasures, and the second is the effect on cognition of ketamine, an agent intended to replace morphine as a battlefield analgesic. The following topics will be covered in the papers presented in this section:

1. John and Lynn Caldwell, in an overview of recent applied military research, discuss the application of sleep-promoting and alertness-enhancing compounds in military operations (1). Guidelines are recommended for the operational use of hypnotics such as temazepam, zolpidem, and zaleplon to enhance sleep when the opportunity arises, and for alertness-enhancing compounds such as caffeine, modafinil, and dextroamphetamine to temporarily support alertness during periods of sustained wakefulness.

2. Laura Rowland, in a review of the clinical applications and potential adverse events, discusses the neurobiological and behavioral effects in humans of ketamine used at subanesthetic doses (3). The current battlefield analgesic, morphine, impairs cognitive performance to the degree that effectiveness is lost after a single dose. Nasal ketamine is under assessment as a battlefield analgesic that may provide a future warfighter with both effective pain control and retained cognitive capability, thereby enabling greater post-injury operational effectiveness. This evaluation of the risks/benefits, its rapid onset, safety profile, and dose-dependent impact on psychotomimetic symptoms argues in favor of its use in military settings.

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